Environmental Tobacco Smoke, Indoor Allergens, and Childhood Asthma

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Both environmental tobacco smoke and indoor allergens can exacerbate already established childhood asthma, albeit primarily through quite disparate mechanisms. In infancy and childhood, environmental tobacco smoke (ETS) exposure is associated with measures of decreased flow in the airways, bronchial hyperresponsiveness, and increased respiratory infections, but the relationship between ETS and allergy is poorly understood. Indoor allergens from dust mite, cockroach, and cat can be associated with asthma exacerbation in children sensitized to the specific allergens. The precise role of either ETS or indoor allergens in the development of asthma is less well understood. The strong and consistent association between ETS and asthma development in young children may relate to both prenatal and postnatal influences on airway caliber or bronchial responsiveness. Dust mite allergen levels predict asthma in children sensitized to dust mite. The tendency to develop specific IgE antibodies to allergens (sensitization) is associated with and may be preceded by the development of a T-helper (Th)2 profile of cytokine release. The importance of either ETS or indoor allergens in the differentiation of T cells into a Th2-type profile of cytokine release or in the localization of immediate-type allergic responses to the lung is unknown. This article evaluates the strength of the evidence that ETS or indoor allergens influence asthma exacerbation and asthma development in children. We also selectively review data for the effectiveness of allergen reduction in reducing asthma symptoms and present a potential research agenda regarding these two broad areas of environmental exposure and their relationship to childhood asthma. *Key words*: allergy, asthma, cat, children, cockroach, dust mite, environmental tobacco smoke, indoor allergens. — *Environ Health Perspect* 108(suppl 4):643–651 (2000).
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In 1992 the U.S. Environmental Protection Agency (U.S. EPA) concluded that environmental tobacco smoke (ETS) is responsible for the induction of new cases of asthma (*1*). In 1997, the Third International Workshop on Indoor Allergens concluded that dust mites must be a major cause of asthma (*2*). Studies consistently demonstrate that both ETS and indoor allergens can exacerbate already established asthma (*3–5*), albeit primarily through quite disparate mechanisms. However, the precise role of either ETS or indoor allergens in the development of asthma is less well understood. In this article we compare and contrast the data regarding the role of these two very different groups of exposures in both the development and the exacerbation of asthma in childhood. Before reviewing the strength of the data that exposure to ETS may influence the course of childhood asthma, it is helpful to review what might be meant by asthma and what is understood about the process of asthma development.

What Is Asthma?

Epidemiologic Definitions

Many working definitions of asthma exist and have been useful for different facets of asthma research. Particularly after 2 years of age, for analytic purposes epidemiologists often accept that a child has asthma if a parent reports a doctor's diagnosis of asthma. Current asthma can be defined as doctor-diagnosed asthma with wheeze in the past year (*6*). The presence of bronchial hyperresponsiveness, if measured, adds to the specificity of the diagnosis (*7*). However, not all individuals with bronchial hyperresponsiveness have asthma. Similarly, although all asthmatics have had bronchial hyperresponsiveness, the level of hyperresponsiveness varies between and within asthmatic children. Less sensitive measures of hyperresponsiveness (e.g., exercise testing) may miss a tendency toward bronchial hyperresponsiveness in a well-controlled asthmatic child.

Measures of allergic sensitization are also used in the definition or description of asthmatic populations. In the United States greater than 80% of asthmatic children have allergy to one or more indoor allergens, but many children with allergy do not have asthma (*8,9*). Occupational asthma is often associated with non–IgE-mediated sensitivity, whereas most documented allergy in childhood asthma is IgE mediated. Children can have doctor-diagnosed asthma with bronchial hyperresponsiveness but without allergy. These children are in the minority in the United States but may be in the majority in communities in rural areas of portions of the world where parasitic infections are common and access to antibiotics for treatment of bacterial infections is limited (*10,11*).

Immunologic Definitions

The immunologic and pathologic definitions of asthma are derived primarily from data regarding well-established clinically diagnosed adult asthmatics or from animal models. The 1997 National Institutes of Health Expert Panel Report on Asthma (*12*) recently provided a working definition of asthma, describing it as a chronic airways disease characterized by bronchial hyperresponsiveness and a link between bronchial hyperresponsiveness and airways inflammation. This inflammation involves many cell types and their proinflammatory products. Longstanding asthma can also involve fixed remodeling of the airway walls. In most U.S. asthmatics the airway inflammation is believed to be, in part, an expression of an allergic response localized to the lung. A simplified presentation of immunology models of adult allergic asthmatic behavior is relevant to this discussion. The established allergic asthmatic response involves the presentation of an allergen by a specialized antigen-presenting cell (dendritic cell) to a T lymphocyte in the lung. If the individual has a T-helper (Th)2 phenotype, the production of certain proinflammatory cytokines (e.g., interleukin (IL)-4, IL-5, IL-13) predominates, leading to the release of IgE from B lymphocytes, other proinflammatory products from mast cells and eosinophils, and ultimately resulting in airway narrowing and asthmatic symptoms. In response to allergen presentation, adults with a Th1 phenotype tend to have more production of interferon gamma (IFN-γ) and cytokines that may not initiate a proinflammatory allergic response (*13,14*). Although useful, the Th1:Th2 dichotomy may be less applicable to allergic asthmatic behavior in young children than to adult asthmatic behavior.

Asthma Development

There is no consensus as to the process by which asthma develops, but a working model of the process is useful in considering where in that process an environmental factor might influence asthma development (Figure 1).

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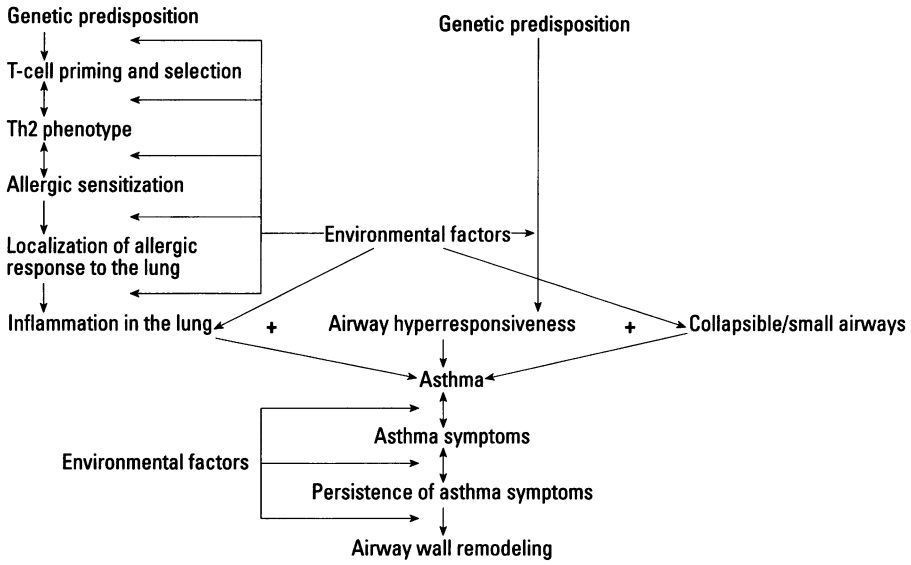

Figure 1. Proposed model for the development of asthma symptoms influenced in part by models presented by Holt and colleagues (*13*).

Models regarding the process by which allergic asthma develops draw on relatively sparse data regarding the evolution of the immune response in early childhood and require further testing. According to the models presented by Holt and colleagues (*13–15*) and Prescott et al. (*16,17*), asthma is preceded by the development of a Th2 phenotype and concurrent or subsequent sensitization. Their data suggest that T-cell priming and selection begins early in life and may begin *in utero*. Normal *in utero* fetal growth without fetal rejection requires a bias toward Th2 behavior according to Wegmann et al. (*18*). Holt and Prescott (*17*) believe that to avoid an allergic phenotype, postnatal immune development may require a transition from a Th2 to either a Th1 or Th0 phenotype (immune tolerance). Simplistically speaking, nonallergic development would be reflected in a transition from the production of primarily Th2 cytokines to the production of primarily Th1 cytokines (e.g., more IFN-γ, less IL-4, IL-5, IL-10, or IL-13). If, instead, selection is toward the maintenance of a Th2 phenotype, sensitization may develop.

The development of allergy is not equivalent to the development of asthma. Allergic asthma probably requires localization of the allergic inflammatory response to the lung and also the development of bronchial hyperresponsiveness. Bronchial hyperresponsiveness has been described as an excessive sensitivity of the airways to a variety of endogenous and/or exogenous bronchoconstrictor agents (*12*). Bronchial hyperresponsiveness appears to be a phenotype distinct and often separable from allergic inflammation even though allergic inflammation can increase bronchial hyperresponsiveness. Distinct genetic and environmental factors may interact to influence the development of allergy, the localization of the allergic response to the lung, and the development of bronchial hyperresponsiveness. Localization of the allergic response to the lung may involve selection of antigen-presenting cell behavior in the lung.

Bronchial hyperresponsiveness may develop independently from allergy-related lung inflammation. Bronchial hyperresponsiveness may precede or occur concurrently with differentiation of the T-cell phenotype, development of sensitization, and localization of the immediate-type allergic response to the lung.

The *in utero* development of lung architecture leading to collapsible or narrowed airways may also influence the tendency to express asthmatic symptoms in childhood. While airway narrowing occurs with airway inflammation and bronchial hyperresponsiveness, alteration of lung architecture (such as may occur with *in utero* tobacco smoke; see below) may be a third somewhat independent phenotype, increasing the risk of expression of asthmatic symptoms.

Gender is important in the timing of asthma development and diagnosis. While the majority of asthma is diagnosed before children enter school (*8,19*), early diagnosis of asthma occurs more in males and later diagnosis occurs more in females (*20*).

Asthmatic symptoms persist in some but not all children and may recur later in adulthood after a quiescent period. Ultimately, in chronic, severe asthmatics, airway wall remodeling may occur, with an irreversible component to the disease.

Family history of asthma is a predictor of asthma in children; genetic factors are presumed to play a role in the development of allergy, bronchial hyperresponsiveness, and asthma (*21*). Geneticists recognize that there will be no one single gene for asthma. The study of the genetics of asthma is complex and involves investigation of a multitude of genetic polymorphisms. Depending on the genetic phenotype of an individual, environmental factors are likely to be more or less influential in the development of asthma or secondary clinical phenotypes such as allergy or bronchial responsiveness. However, the study of gene-by-environment interactions may be difficult, requiring large, appropriately selected populations and appropriately timed collection of measures of environmental exposures.

In addition to considering environmental exposures as risk factors for development of asthma, it is also important to consider environmental exposures that may be protective factors. The same environmental exposure can be a risk factor, a protective factor, or not influential, depending on the host and his stage of development.

Environmental Tobacco Smoke

Prenatal versus Postnatal ETS Exposure: Differences in Physiologic Effects

The chemical and physical properties of ETS are well described in the 1992 U.S. EPA document on the respiratory health effects of passive smoking (*1*). The distinction between prenatal and postnatal smoking is important, since the route of exposure and the consequences of exposure differ. The smoking product nicotine (*22*) is known to cross the placenta. It is likely that many of the other chemical components of maternal cigarette smoking also influence either placental health or fetal growth. In infants, prenatal smoke exposure is also associated with deficits in forced expiratory flow at functional residual capacity (*23*) and with an index of tidal respiratory flow (time to peak expiratory flow as a fraction of total expiratory time) (*23,24*). The ETS-associated reduction in flow is believed to represent a reduction in airway size (*25*), possibly resulting from a change in lung architecture. Animal studies have demonstrated that *in utero* ETS exposure in rats is associated with reduced elastic fibers in the fetal lung (*26*). An Australian study also found an association between *in utero* tobacco exposure and bronchial reactivity in infants (*27*); whether the effect on bronchial responsiveness is independent of airway size is not known.

Postnatal ETS as a lung irritant has proinflammatory effects on the airways. In addition to its prenatal association with reduced airway size and its postnatal behavior as a proinflammatory lung irritant, some have proposed that ETS may also influence the development of allergy. Studies have not consistently demonstrated associations between prenatal

maternal smoking and cord IgE levels (*28–30*). Nevertheless, maternal smoking has been associated with elevated serum IgE levels in infants (*31,32*) and increased prevalence of skin-prick test responses in children (*33*).

ETS and Exacerbation of Asthma

Data strongly support the association of ETS with asthma severity and increased bronchial responsiveness in asthmatic children. These data were reviewed by Strachen and Cook (*34*) as well as in the U.S. EPA document (*1*). A New York study of 191 asthmatic children 4–17 years of age found a correlation between the number of emergency room visits and cigarette smoke exposure ($p = 0.008$); the mean frequency (± SD) of annual emergency room visits for children exposed to ETS was 3.1 ± 0.4, compared with a mean frequency of 1.8 ± 0.3 for children from nonsmoking homes (*35*). An east Boston study found that the change in forced expiratory volume in 1 sec (FEV_1) induced by subfreezing air was significantly higher in asthmatic subjects whose mothers smoked at least one cigarette per day than in those asthmatics whose mothers were nonsmokers (*36*). In a study of 415 nonsmoking children 1–17 years of age referred to an allergy clinic in Canada for asthma or recurrent wheeze, children of smoking mothers had significantly higher indices of asthma severity and significantly lower FEV_1 than children of nonsmoking mothers. They also had significantly more hyperresponsiveness to histamine. Interestingly, the effect was stronger for older children (12–17 years of age) than for children 6 years of age or younger (*37*). Seasonal fluctuations in urinary cotinine in children exposed to ETS (*38*) and in the effects of passive smoking on asthma severity (*37*) suggest that ETS effects on asthma severity may be reversible and that decreasing ETS exposure could prevent asthmatic attacks.

Acute respiratory infections are among the most common triggers for the exacerbation of asthma. In epidemiologic studies most acute lower respiratory illnesses (croup, bronchitis, bronchiolitis, or pneumonia) are presumed to be viral or bacterial in etiology, but documentation of the viral pathogen is usually not possible. Numerous studies demonstrate the association between ETS exposure in the home and acute respiratory illnesses in childhood; key studies are presented in the Surgeon General's report (*39*), the National Research Council's report (*40*), and the U.S. EPA report (*1*).

Important in the distinction between prenatal and antenatal smoking effects are the studies by Chen and co-workers (*41–43*) reporting increased risk of acute respiratory illnesses in Chinese children living with smoking fathers but not with smoking mothers. Although the risk of ETS-associated acute lower respiratory illness diminishes with age, in school-age children associations are still found between ETS and acute respiratory illnesses significant enough to keep children home from school (*44*). It is likely that the associations between postnatal ETS and asthma severity are, in great part, mediated through the propensity for ETS to increase the risk of the expression of clinically significant acute respiratory infections.

In chamber studies of specifically sensitized asthmatic subjects, irritant gases such as nitrogen dioxide (NO_2) and ozone potentiated the early or late asthmatic response to inhalation of allergen (*45–47*). Acute exposure to ETS may also potentiate the asthmatic response to allergen inhalation (*31*), but few studies exist to support this hypothesis.

ETS and Asthma Development

ETS, particularly maternal smoking, increases the risk of wheeze in children under 6 years of age (*31,48–52*). This strong and consistently noted relationship between passive smoking and wheeze is believed to be secondary to *a*) the prenatal effect of maternal smoking on reduced flow, likely related to prenatal alterations in airway architecture and/or bronchial hyperreactivity, and *b*) the irritant postnatal smoking effects. Cross-sectional studies suggest that the association between maternal smoking during pregnancy and spirometric evidence for small airways (reduced flow as measured by forced expiratory flow between 25 and 75% of forced vital capacity persists into the school-age years (*53,54*), adding to the physiologic plausibility of the epidemiologic association between maternal smoking during pregnancy and later wheeze or asthma. ETS (pre- and postnatal) also increases the risk of symptomatic acute lower respiratory illnesses (*1*) and may interact with certain viral illnesses in increasing the risk of asthma development.

Although ETS (particularly maternal smoking) is also consistently associated with new incidence or prevalence of asthma in children less than 6 years of age (*31,34*), estimates for associations between ETS and asthma in school-age children tend to be smaller in magnitude and less precise. As children grow and airway size increases, it is likely that the effects of maternal smoking on lung architecture are less influential than the effects of other factors on inflammation in the lung airways or bronchial reactivity in the expression of asthma. In addition, the irritant effects of parental ETS are less likely to influence schoolchildren, who spend less of their day in contact with smoking parents. As noted above, we do not know whether there are effects of prenatal or postnatal ETS on allergic sensitization, selection of the T-cell phenotype, or priming of the lung.

Research Agenda

The role of ETS (pre- or postnatal) in the development of allergy and in the potentiation of the immune response to allergen merits further investigation. As previous authors have noted (*25,31*), this will require better markers of the development of IgE-mediated allergy in early childhood, and markers of specific genetic predisposition. Because sufficient evidence for associations between ETS and wheeze/asthma already exists, we should also focus on efforts to reduce parental smoking, particularly maternal smoking. The effectiveness of parental smoking cessation trials and of asthma education have been recently reviewed (*3*). Unfortunately, smoking among women and girls is actually increasing in some socioeconomic and cultural groups, and efforts to develop culturally specific educational campaigns against smoking will benefit parents and children.

Allergens and Asthma

Childhood asthma is usually associated with allergy to one or more indoor and outdoor allergens. The allergens to which the asthmatic children respond reflect the ecology of their community. For example, in many parts of Australia and New Zealand, the predominant indoor allergen is dust mite, to which most asthmatics are sensitized (*55,56*). Among economically disadvantaged populations in the Northeastern United States and in Virginia, one of the predominant allergens is cockroach (*57*); therefore, more than 50% of asthmatics are sensitized to this source of allergens. Very little sensitization from exposure to dust mite was noted among asthmatic children in Los Alamos, New Mexico, and Tucson, Arizona, where asthmatic children tended to be sensitized to cat (*58*) or Alternaria (*59*). The fact that more than 80% of childhood asthmatics in the United States are allergic does not necessarily mean that the allergens caused their asthma. However, the data consistently suggest that if asthmatics are specifically sensitized to a particular allergen, exposure to high levels of that allergen may exacerbate their asthmatic symptoms.

The literature on the indoor allergens and their relationship to sensitization and asthma was recently reviewed in the "Report of the Third International Workshop on Indoor Allergens and Asthma" (*2*). Many of the biologic agents that can be sources of allergens are listed in that review. It is important to be aware that many of these potential sources of exposure may contain not only allergens but also irritants or toxins. The immunochemistry, molecular biology, and ecology of many of these agents are reviewed in the workshop report and will not be discussed at length in this present article except in relationship to differences

that influence the mode of exposure or the nature of the allergic or irritant response. In the following section, we review the literature exploring dust mite, cockroach, and cat allergens as either sources of asthma exacerbation or as cofactors in the development of asthma. We also review the data regarding allergen avoidance for each of these allergens, whose sources and mode of dissemination differ. The literature on asthma and fungi, which can be indoor as well as outdoor allergens, is reviewed by Burge and Rogers (*60*).

Dust Mite

Biology and Ecology

While at least 12 dust mite allergens have been identified (*2*), Der p 1 and Der f 1 are the dust mite allergens most commonly assessed in their associations with home characteristics and with health outcomes. Mite reproductive responses to humidity are temperature dependent (*61*). Dust mite is uncommon at high altitudes and in dry, cold northern climates (*2*). In Boston, Massachusetts, Der f 1 and Der p 1 were more prevalent in single-family homes than in apartments, possibly because apartments tend to be hotter and drier in the New England winters. Although inner-city homes in the Northeastern United States have less dust mite and more cockroach allergen (*62*), homes of asthmatics from disadvantaged communities in the Southern United States have both dust mite and cockroach allergens (*63,64*). These differences are likely primarily related to differences in temperature and humidity. The species and quantity of mite are dependent on not only humidity and temperature but also on the presence of food for the mite (e.g., skin scales) and material in which the mites can breed. Reservoirs of dust mite allergens include bedding, mattresses, carpets, upholstered chairs, and sofas (*2*).

In the absence of experimental or household disturbance, most investigators have been unable to detect airborne mite (*2*). Most exposure is likely to occur when the individual contacts and disturbs the dust on the surfaces and in the materials where the mites breed.

Most published data on the health effects of dust mite allergen are based on the measurement of the allergen concentration in micrograms per gram of dust. Although the concentration of dust mite is usually closely correlated with the amount of dust collected in a standard protocol (*65*), the amount of dust collected and the absolute weight of allergen collected may be useful in evaluating the success of intervention trials to reduce allergen load (*2*).

Dust Mite Allergen and Exacerbation of Asthma

Of the indoor allergens, dust mite has been studied most extensively (Table 1). Dust mite has been demonstrated to play a role in exacerbating asthmatic symptoms in specifically sensitized individuals. The strongest evidence for dust mite as a trigger of asthma comes from the long-term dust mite avoidance literature (*2*). Dust mite levels are low at high altitude. After 5 weeks at high altitude in Switzerland, 14 asthmatic children had reduction of bronchial obstruction, bronchial hyperresponsiveness to exercise, eosinophilia, and peripheral blood T-cell activation (*66*). In 20 children with asthma and allergy to dust mite, after 40 and 80 days of antigen avoidance at high altitude in Italy, bronchial hyperresponsiveness and serum IgE were reduced; however, they quickly increased 15 days after return to sea level (*67*). Some studies also suggest that long-term reduction of dust mite levels in bedrooms may improve symptoms in mite-allergic asthmatics (*68,69*). In a study of 24 mite-allergic asthmatics, a 98% reduction of mite levels by encasing mattresses and pillows resulted in reduction in bronchial hyperresponsiveness after 8 months (*68*).

Dust Mite Allergen and Asthma Development

For children who are already allergic to other allergens, level of dust mite allergen has predicted development or persistence of specific sensitization to dust mite. Kuehr et al. (*70*) enrolled 1,812 German primary school children in a population-based 2-year follow-up study. In three consecutive skin prick tests, each 12 months apart, sensitization to Der p and six non-Der p allergens was ascertained. The level of Der p in the bed mattresses was measured. In children with prior sensitization to other allergens, exposure to Der p above a level of 9 μg/g significantly increased the risk of incident sensitization to Der p 1. However, in previously nonallergic populations (children without any prior evidence of sensitization to other allergens), only levels greater than 80 μg/g increased the risk of new sensitization to Der p 1 (*70*). In another prospective study, Wickman and Korsgaard (*71*) followed 155 children from Sweden with positive skin tests to house-dust mite to evaluate whether dust mite levels in the children's mattresses predicted conversion from a status of skin test positive to skin test negative in reaction to dust mite. Low exposure to dust mite predicted conversion from skin test positive to skin test negative (*71*). In an English study of 66 children with at least one atopic parent, bedroom floor dust levels of Der p 1 in children 1 year of age predicted sensitization to dust mite by age 5, as measured by skin test positivity, IgG, or IgE, though IgG was the most sensitive outcome (*72*).

For children sensitized to dust mite, the risk of having current asthma doubled with every doubling of Der p 1 level in a cross-sectional study of children 8–11 years of age from six different regions in New South Wales, Australia (*56*). In a birth cohort study of 67 British children of allergic or asthmatic parents, the relative risk of asthma in children 11 years of age was 4.8 for children exposed to more than 10 μg/g Der p 1 in infancy (*73*). The age of wheeze onset was inversely related to the level of dust mite in the home in infancy. Dust mite levels at 11 years of age did not predict asthma at age 11.

These data strongly suggest that dust mite exposure is a risk factor for the development of symptomatic asthma in children with prior allergy. We are not certain about the role of dust mite and other allergens in immune deviation toward a Th2 phenotype, in localization of the allergic immune response to the lung, or in the initial expression of the phenotype of bronchial hyperresponsiveness.

Cockroach

Biology and Ecology: Measurement of Cockroach and Its Allergens

The distribution of cockroaches and their allergens in the home directly relates to the distribution of water and food (*74*). Water is essential for cockroach survival, but all except the smallest species can survive 2–3 weeks without water or food. Cockroach populations are generally higher in kitchens (*65*). However, particularly at night, they will migrate to bathrooms or sleeping areas in search of water and have been known to drink from the eyes and nostrils of sleeping children (*75*). Cockroaches are omnivorous and eat many human foods, as well as vegetable fibers, inks, and animal-based glues. They also can obtain water from the moisture absorbed by old paper, making newspaper in kitchen cupboards a source of food and water for the insects.

In the United States, cockroaches and their allergens are more prevalent in southern, humid climates than in dry, western climates. In the Northeastern United States, high cockroach allergen levels have been associated with urban residence, low socioeconomic status, and living in an apartment compared with a single-family home (*62,65,76*).

As with dust mite, the biology of the cockroach is relevant to measurement and control issues (*77*). For example, according to Hemingway and Small (*78*), the use of organophosphate insecticide may result in insecticide resistance through the production of a scavenging enzyme, glutathione *S*-transferase, which is itself a potent allergen.

Table 1. Selected literature on dust mite, asthma exacerbation, and asthma development.

Author	Geographic location	Population	Study design	Outcome
Simon et al., 1994 (*66*)	Switzerland	14 sensitized asthmatic children	Prospective avoidance trial	Reduction of bronchial hyperresponsiveness, eosinophilia
Piacentini et al., 1993 (*67*)	Italy	20 sensitized asthmatic children	Prospective avoidance trial	Reduction of bronchial hyperresponsiveness, serum IgE
Ehnert et al., 1992 (*68*)	Germany	24 sensitized asthmatic children with bed dust mite	Prospective avoidance trial	Reduction of bronchial hyperresponsiveness
Carswell et al., 1996 (*69*)	England	49 sensitized asthmatic children with bed dust mite	Prospective avoidance trial	Reduction of bronchial reactivity, FEV_1, medication use, symptoms
Kuehr et al., 1994 (*70*)	Germany	1,812 school children	Prospective	Sensitization to dust mite
Wickman and Korsgaard, 1996 (*71*)	Sweden	155 school children	Prospective	Loss of dust mite skin reactivity
Peat et al., 1996 (*56*)	Australia	80 school children per region from 6 regions	Cross-sectional	Bronchial hyperresponsiveness Current asthma
Sporik et al., 1990 (*73*)	England	67 children of asthmatic/allergic parents	Prospective	Asthma

The most common cockroaches in the United States are the German cockroach (*Blattella germanica*) and the American cockroach (*Periplaneta americana*). We recently reviewed the literature on the allergens associated with these two species in a discussion of cockroach allergy and asthma (*76*). Bla g 1, 2, and 4 are three major German cockroach allergens that have been identified. Bla g 1 is also found in the American cockroach. In Virginia, 30% of cockroach-allergic patients had IgE specific for Bla g 1, 60% had IgE specific for Bla g 2, and up to 60% had IgE specific for Bla g 4 (*79,80*).

In the National Inner City Asthma Study, Bla g 1 was detected in the bedrooms of 404 of 476 (85%) of urban asthmatic children (*62*). Although signs of cockroaches in the previous month is a strong predictor of measurable cockroach allergen, detectable Bla g 1 or 2 was measured in 48% of homes, and levels greater than 2 U/g were measured in 7% of homes without signs of cockroaches in a sample of 499 urban and suburban Boston homes (*65*).

Like dust mite, most cockroach allergen is only transiently airborne for a short time after disturbance (*81*). In the case of cockroach allergen, this relates to the large size of the particles with which the allergen is associated. Dust levels of cockroach allergen are only an approximate measure of the potential for cockroach allergen exposure. The vacuuming of a single cockroach and its feces can result in measurement of a high level of allergen, even if few cockroaches are in the room. On the other hand, cockroaches are often present in crevices, and the vacuuming of the center of a room without vacuuming of crevices may result in the underestimation of potential exposure.

Cockroach Allergen and Exacerbation of Asthma

Asthmatic patients who have positive skin tests to cockroach extract tend to develop an acute and late asthmatic response to inhalation of cockroach extract aerosol, whereas asthmatic patients without specific sensitization to cockroach extract do not (*82,83*). In asthmatic children specifically sensitized to cockroach allergen, Bla g 1 levels greater than 8 U/g dust were associated with higher hospitalization rates, more unscheduled medical visits, and more parent-reported wheezing (*62*). Cockroach allergen level was not a risk factor for asthma exacerbation in children not specifically sensitized to cockroach allergens. In a cross-sectional Baltimore, Maryland, study of 87 children with atopic asthma, cockroach allergen level in the home was a predictor of skin reactivity to cockroach (*84*). Thus the predominant allergen in the home may influence the specific allergen to which atopic asthmatics become sensitized.

Cockroach Allergen and Asthma Development

Whether cockroach antigen level predicts the risk of incident asthma in children already allergic and specifically sensitized to cockroach is unknown. In a birth cohort study of 499 children of allergic or asthmatic parents, detectable cockroach allergen in the family room was a predictor of repeated wheeze in the first year of life (*85*). Fewer than half of those with repeated wheeze in the first year of life develop asthma (*52*). Particularly if they have small airways, children who wheeze in infancy are often responding to proinflammatory stimuli through nonallergic mechanisms. It is not known whether the cockroach-associated wheeze in this early life study represents a nonallergic or an allergic response to cockroach.

Cockroach Allergen Avoidance

A recent review presents a detailed discussion of avoidance measures, including abamectin gel baits and bait stations, vacuuming, washing surfaces, sealing cracks, washing dishes, and sealing food (*76*). Preliminary data from studies of the effects of pest control and cleaning on allergen levels suggest little immediate success of these measures in reduction of levels to below those associated with asthma exacerbation in sensitized children (*86*). Allergen may take a long time to degrade and may continue to leach from cracks and crevices where fecal material was deposited.

Animals: Cat

Biology and Ecology: Measurement of Cat and Its Allergens

The major cat allergen Fel d 1 is found on cat hair and is produced in cat sebaceous, salivary, and anal glands (*87*). In contrast with cockroach allergen, which is only airborne during disturbance of household dust, cat allergen in association with particles such as dander is easily airborne. Cat allergen is also very adherent. Consequently, cat allergen is easily spread throughout a house, even when cats are kept out of certain rooms. Moreover, cat allergen is easily carried from home to home, office, school, or day-care center by those who touch cats or visit households with cats (*88–90*). At trace or small amounts that may be significant for sensitization or exacerbation of disease in sensitized individuals, Fel d 1 is found in most noncat homes (*65,91*), though allergen levels are generally higher ($\geq$ 8 μg/g) in homes with cats.

Cat Allergen and Exacerbation of Asthma

Exposure to inhaled cat allergens can lead to bronchial hyperresponsiveness in specifically allergic asthmatic subjects (*92*). Norman and colleagues (*93*) documented progressive increases in both nasal and lung symptom scores during a 60-min period in a cat room. For cat and cockroach, the combination of sensitization and the presence of allergen in the house was associated with asthma presenting to hospital (*63*).

In a cross-sectional New Mexico study of children with asthma or bronchial hyperresponsiveness, cat sensitization and exposure to cat allergen were common (*58*). However, no relationship was found between sensitization or symptoms and the current level of allergen in the home (*94*).

Cat Allergen and Asthma Development

No studies suggest associations between elevated cat allergen levels in the home and the development of asthma. In a longitudinal New Zealand study, sensitization to cat predicted development of asthma in children (*95*); sensitization to cat predicted development of bronchial hyperresponsiveness in a study of adults in Boston (*21*). A recent cross-sectional Swedish study suggests an inverse relationship between the presence of a cat or dog in the first year of life and the presence of both sensitization to cat and asthma by 13 years of age (*96*).

Cat Allergen Avoidance

Because cat allergen is everywhere, there is little potential for absolute avoidance (*88,90*). The relative importance of home versus community-wide exposure to cat allergen in risk of specific sensitization to cat is unknown. Because of the reluctance of cat-allergic symptomatic asthmatics to remove their cats from the home, a number of recent studies have focused on the potential for lowering cat allergen levels by washing the cat, use of HEPA filters, and/or removal of the cat from the bedroom (*97*). The effectiveness of any of these measures in reducing asthma symptoms or improving lung function is unproven and requires further evaluation. Although washing cats by immersion will transiently remove significant allergen from the cat and reduce the quantity of airborne Fel d 1, this reduction in allergen may not be maintained by 1 week (*98*). In an intervention trial combining HEPA filter use, mattress covers, and exclusion of the cat from the bedroom, a Maryland study detected no improvement in daily symptom scores, peak flow rates, medication use, spirometry, bronchial hyperreactivity, or cat-specific IgE levels in cat-allergic subjects (*97*). However, airway hyperresponsiveness was improved and peak flow variation was decreased during the use of air cleaners in a double-blind, placebo-controlled, crossover study of 20 asthmatic children sensitized to cat or dog allergens (*99*). Even when the owner removes the cat, cat allergen levels may remain elevated for many months (*100*). For highly sensitive individuals, removal of carpets and upholstery, and encasement of mattresses may be required for diminishing cat allergen levels sufficiently to adequately reduce allergic symptoms.

Other Animals: Dogs, Rodents, Farm Animals (Horses, Cows, Swine)

These animals are also sources of allergens (*79*) and depending on the ecology of the community, sensitization to these animals can also be associated with asthma. For instance, in New Mexico dog as well as cat sensitization was associated with asthma (*94*). In the inner-city asthma study, 19% of asthmatics were allergic to rat and 15% were allergic to mouse (*62*). Allergy to cow and horse hair can be found among veterinarians, farmers, and their families (*79*).

In dog-sensitized asthmatics, dog allergen can be associated with bronchial hyperreactivity. In a cross-sectional Finnish study of 203 asthmatic children, allergy to dog and keeping a dog were associated with a positive bronchial provocation test with dog allergen (*101*). Although the Finnish study also suggested that keeping a dog in early life was a risk factor for asthma, the cross-sectional European Community Respiratory Health Survey of more than 13,000 adults found that among those without allergic parents, a report of keeping dogs in childhood was associated with a lower risk of asthma (*102*).

Animals as a Source of Endotoxin

Animals can also be a source of endotoxin, which has been proposed both as a source of protection against the development of asthma and as an irritant that may exacerbate asthma (*103*). A Belgian study suggested an interaction between endotoxin and dust mite levels in the exacerbation of asthma in dust mite-sensitized asthmatics (*104*).

Both German and Swiss studies suggest cross-sectional associations between living on the farm and decreased risk of asthma (*105,106*). The farm environment is complex and the factors responsible for the decreased asthma risk are unknown. The authors hypothesize that exposure to endotoxin early in life may be protective against asthma development, and that there may be a gene-by-environment interaction in creating tolerance.

Research Agenda: Indoor Allergens

Biology and Ecology

Further work is needed to define the structure and biologic function of the allergens judged to be important in human sensitization and in the triggering of asthma (*2*). An allergen can be defined as important in human sensitization if it accounts for a significant proportion of the animal- or insect-specific IgE and T-cell responses in humans (*2,79*). Allergen control strategies would also be advanced through further understanding of factors influencing dust mite and cockroach reproduction and allergen production by the various animal sources of allergen.

Further standardization of allergen assays is recommended (*2*) to improve the comparability of epidemiologic observational and intervention studies. The relative importance of factors that can lead to laboratory measurement error in estimation of allergen level should be explored. Various substances in dust can influence allergen assays (*107*). At very high or very low levels, the precision of the estimates for allergen levels can decrease significantly. Knowing the 95% confidence limits around an estimate can facilitate evaluation of whether a control measure has significantly lowered allergen levels.

Allergen level has generally been described in micrograms per gram or units per gram. Particularly in intervention trials in which dust is sampled according to standard protocols (but also in observational epidemiologic studies), investigators should further explore expressing allergen in terms of absolute grams of allergen collected. Not only the concentration of allergen but also the amount of allergen-containing dust may influence asthma severity.

More work is needed to assess the optimal and most cost-effective mode of sampling allergen to best represent exposure. Optimal sampling methods will vary depending on the animal/insect behavior of the allergen source and depending on the size and aerodynamics of the particle-associated allergens. Air sampling may be a better representation of exposure than dust sampling for some allergens (e.g., fungi), but investigators need to evaluate the practical issues related to performing representative air sampling over prolonged periods of time. Brief periods of air sampling may be useful for assessing the levels of some allergens (e.g., cat), but not for others.

The location of sampling needs further evaluation. For example, with cockroach allergen, sampling can be performed in areas where the insect is suspected to live (e.g., in cracks in walls, in furniture), in common living areas where human exposure may take place (e.g., kitchen), or in sleeping areas.

Development of recombinant allergens with the same biologic activity as the parent allergen will prove useful for improving the comparability of assays, for immunotherapy, and for evaluation of T-cell responses to allergen.

Investigators should further explore the potential for allergen sources (e.g., fungi, dust mites, cockroaches, large animals) to be sources of toxins and lung irritants as well. It is possible that the effects of allergens, toxins, or irritants will vary according to the genetics of the host. The response of the host to allergens, toxins, or irritants may also vary according to the level of exposure, the mode of exposure (e.g., gut or lung), and the age of exposure (e.g., when exposure occurs in relationship to the development of sensitization or asthma development).

Allergens and Exacerbation of Asthma

The potential for allergen to trigger asthma in specifically sensitized subjects has been more

fully explored for some allergens (e.g., Fel d 1) than for others (e.g., Can f 1, mouse and rat allergens). Epidemiologic and laboratory chamber studies should further explore in specifically sensitized individuals whether asthma severity is predicted by exposure to allergens other than cat, dust mite, or cockroach. Further work is needed to investigate whether nonallergenic pollutants (e.g., NO_2, O_3, or particles) potentiate the response to allergen inhalation in specifically sensitized individuals.

Programs in asthma education currently appropriately target recommendations regarding alterations in home characteristics to avoidance of allergens to which the asthmatics are currently sensitized. For example, asthmatics allergic to dust mite and not cat are not asked to get rid of their cats. Investigators need to further evaluate the success of asthma avoidance programs in achieving participant compliance, the reduction of allergen, and the reduction of asthma severity. Studies should also investigate the potential of continued allergen exposure to specifically sensitize asthmatics to the allergen. That is to say, if an allergic asthmatic child who is not sensitized to cat continues to be exposed to cat, what is the risk that sensitization will occur? If sensitization occurs, then the cat may ultimately become a risk factor for asthma severity.

Several troublesome questions regarding allergen avoidance remain unanswered to some extent. If allergic asthmatics avoid the indoor allergens to which they are sensitized, will their asthma improve, or will they just become sensitized and symptomatic to other allergens in the environment? The answer to this question may differ by genetic phenotype. For specifically sensitized individuals, what is the significance of unavoidable allergen exposure at low levels? Here again, the answer may vary by genetic phenotype.

The age of exposure to sources of allergen and genetic phenotype may affect the risk that a specific allergen at a specific level of exposure is a risk factor for asthma exacerbation. As the study of the genetics of asthma evolves, exploration of gene-by-environment interaction may result in our ability to target certain asthmatic children for focused interventions that are more likely to succeed in reducing asthma severity.

Allergens and Asthma Development

In Westernized societies the expression of asthma usually requires the development of allergy, the localization of the allergic inflammatory response to the lung, and the development of bronchial hyperreactivity. Abnormal lung architecture may also contribute to asthma development. The data reviewed in this article suggest that in already allergic populations, indoor allergen exposure may increase the risk of sensitization to a specific allergen. In allergic populations, indoor allergen exposure may also increase the risk of the expression of asthma or the persistence of asthmatic symptoms to the point of being labeled asthmatic.

The role of allergen exposure in the development of allergy—in initial T-cell priming and deviation toward a Th2 phenotype—is poorly understood, as is the role of allergen in the localization of the allergic inflammatory response to the lung.

Further research is needed to explore the early-life process leading to the development of the allergic or nonallergic (tolerant) phenotype, the localization of the allergic response to the lung, and the development of bronchial hyperreactivity. For tolerance to develop, an antigen must be encountered. The question is, what factors influence the mode of recognition and handling of the antigen once it is encountered? And what factors influence the recognition and handling of antigen in the lung? Genetic factors are surely influential and need further exploration. It is likely that a multitude of genetic factors will be defined that influence the recognition and handling of antigens and the expression of bronchial reactivity. The relationship of the most influential of these factors to environmental exposure will be difficult but important to sort out. Many environmental factors have been proposed as potential influences on the development of asthma, through influencing the development of allergy, the expression of allergy in the lung, or the expression of bronchial reactivity. In addition to allergens and ETS, among risk factors proposed as environmental influences on the development of asthma are early-life infections, antibiotic use, vaccination practices, exposure to endotoxin (lipopolysaccharide), exposure to chronic parasitism, factors influencing gut flora, diet (*15*), obesity, a sedentary indoor lifestyle (*108*), and stress. Further research is needed to evaluate the relative importance of these factors in influencing the development of asthma.

References and Notes

1. U.S. EPA. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. EPA/600/6-90/006F. Washington, DC:U.S. Environmental Protection Agency, 1992.
2. Platts-Mills TAE, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor Allergens and Asthma: Report of the Third International Workshop. J Allergy Clin Immunol 100:S1–S24 (1997).
3. Clark NM, Brown RW, Parker E, Robins TG, Remick DG Jr, Philbert MA, Keeler GJ, Israel BA. Childhood asthma. Environ Health Perspect 107(suppl 3):421–429 (1999).
4. Eggleston PA, Buckley TJ, Breysse PN, Wills-Karp M, Kleeberger SR, Jaakkola JJ. The environment and asthma in U.S. inner cities. Environ Health Perspect 107(suppl 3):439–450 (1999).
5. Institute of Medicine. Clearing the Air: Asthma and Indoor Air Exposures. Washington, DC:National Academy Press, 2000.
6. Epidemiology Standardization Project II. Recommended respiratory disease questionnaires for use with adults and children in epidemiologic research. Am Rev Respir Dis 118:7–54 (1978).
7. Carey VJ, Weiss ST, Tager IB, Leeder SR, Speizer FE. Airways responsiveness, wheeze onset, and recurrent asthma episodes in young adolescents. The East Boston Childhood Respiratory Disease Cohort. Am J Respir Crit Care Med 153:356–361 (1996).
8. Croner S, Kjellman NI. Natural history of bronchial asthma in childhood. A prospective study from birth up to 12-14 years of age. Allergy 47:150–157 (1992).
9. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 325:1067–1071 (1991).
10. Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E, Britton J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia [See Comments]. Lancet 350:85–90 (1997).
11. Odhiambo JA, Ng'ang'a LW, Mungai MW, Gicheha CM, Nyamwaya JK, Karimi F, Macklem PT, Becklake MR. Urban-rural differences in questionnaire-derived markers of asthma in Kenyan school children. Eur Respir J 12:1105–1112 (1998).
12. Murphy S. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. NIH Publ 97-4051. Bethesda, MD:National Heart, Lung and Blood Institute, 1997.
13. Holt PG, Sly PD. Allergic respiratory disease: strategic targets for primary prevention during childhood [Editorial; See Comments]. Thorax 52:1–4 (1997).
14. Holt PG. Potential role of environmental factors in the etiology and pathogenesis of atopy: a working model. Environ Health Perspect 107(suppl 3):485–487 (1999).
15. Holt PG, Macaubas C, Sly PD. Strategic targets for primary prevention of allergic disease in childhood. Allergy 53:72–76 (1998).
16. Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, Loh R, Sly PD, Holt PG. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. J Immunol 160:4730–4737 (1998).
17. Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children [See Comments]. Lancet 353:196–200 (1999).
18. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? [See Comments]. Immunol Today 14:353–356 (1993).
19. Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. Am J Epidemiol 132:83–95 (1990).
20. Skobeloff EM, Spivey WH, St. Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. JAMA 68:3437–3440 (1992).
21. Litonjua AA, Sparrow D, Weiss ST, O'Connor GT, Long AA, Ohman JL Jr. Sensitization to cat allergen is associated with asthma in older men and predicts new-onset airway hyperresponsiveness. The Normative Aging Study. Am J Respir Crit Care Med 156:23–27 (1997).
22. Jordanov JS. Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on 1st day of life. Eur J Pediatr 149:734–737 (1990).
23. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, Weiss ST, Speizer FE. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 145:1129–1135 (1992).
24. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 348:1060–1064 (1996).
25. Hanrahan JP. Antenatal interventions in childhood asthma. Eur Respir J 12:46s–51s (1998).
26. Collins MH, Moessinger AC, Kleinerman J, Bassi J, Rosso P, Collins AM, James LS, Blanc WA. Fetal lung hypoplasia associated with maternal smoking: a morphometric analysis. Pediatr Res 19:408–412 (1985).
27. Young S, Le Souef PN, Geelhoed GC, Stick SM, Turner KJ, Landau LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. N Engl J Med 324:1168–1173 (1991) [published erratum appears in N Engl J Med 325(10):747 (1991)].
28. Magnusson CG. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. J Allergy Clin Immunol 78:898–904 (1986).
29. Michel FB, Bousquet J, Greillier P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic diseases in infancy. J Allergy Clin Immunol 65:422–430 (1980).

30. Halonen M, Stern D, Lyle S, Wright A, Taussig L, Martinez FD. Relationship of total serum IgE levels in cord and 9-month sera of infants. Clin Exp Allergy 21:235–241 (1991).
31. Tager IB. Smoking and childhood asthma-where do we stand? [Editorial; Comment]. Am J Respir Crit Care Med 158:349–351 (1998).
32. Kjellman NI. Effect of parental smoking on IgE levels in children [Letter]. Lancet 1:993–994 (1981).
33. Weiss ST, Tager IB, Munoz A, Speizer FE. The relationship of respiratory infections in early childhood to the occurrence of increased levels of bronchial responsiveness and atopy. Am Rev Respir Dis 131:573–578 (1985).
34. Strachan DP, Cook DG. Health effects of passive smoking. 6: Parental smoking and childhood asthma: longitudinal and case-control studies. Thorax 53:204–212 (1998).
35. Evans D, Levison MJ, Feldman CH, Clark NM, Wasilewski Y, Levin B, Mellins RB. The impact of passive smoking on emergency room visits of urban children with asthma. Am Rev Respir Dis 135:567–572 (1987).
36. O'Connor GT, Weiss ST, Tager IB, Speizer FE. The effect of passive smoking on pulmonary function and nonspecific bronchial responsiveness in a population-based sample of children and young adults. Am Rev Respir Dis 135:800–804 (1987) [Published erratum appears in Am Rev Respir Dis 136 (2):532 (1987)]
37. Murray AB, Morrison BJ. Passive smoking by asthmatics: its greater effect on boys than on girls and on older than on younger children [see comments]. Pediatrics 84:451–459 (1989).
38. Chilmonczyk BA, Knight GJ, Palomaki GE, Pulkkinen AJ, Williams J, Haddow JE. Environmental tobacco smoke exposure during infancy. Am J Public Health 80:1205–1208 (1990).
39. U. S. Department of Health and Human Services. The health consequences of involuntary smoking. A report of the Surgeon General. PHS Publ no. 87-8398. Washington, DC:U.S. Public Health Service, 1986.
40. National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC:National Academy Press, 1986.
41. Chen Y, Li WX. The effect of passive smoking on children's pulmonary function in Shanghai. Am J Public Health 76:515–518 (1986).
42. Chen Y, Li WX, Yu SZ, Qian WH. Chang-Ning epidemiological study of children's health. I: Passive smoking and children's respiratory diseases. Int J Epidemiol 17:348–355 (1988).
43. Chen Y, Rennie DC, Dosman JA. Influence of environmental tobacco smoke on asthma in nonallergic and allergic children. Epidemiology 7:536–539 (1996).
44. Gold DR, Rotnitzky A, Damokosh AI, Ware JH, Speizer FE, Ferris BG Jr, Dockery DW. Race and gender differences in respiratory illness prevalence and their relationship to environmental exposures in children 7 to 14 years of age. Am Rev Respir Dis 148:10–18 (1993).
45. Strand V, Rak S, Svartengren M, Bylin G. Nitrogen dioxide exposure enhances asthmatic reaction to inhaled allergen in subjects with asthma. Am J Respir Crit Care Med 155:881–887 (1997).
46. Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, Szalai JP, Raizenne M, Slutsky AS, Zamel N. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects [See Comments]. Lancet 338:199–203 (1991).
47. Molfino NA, Slutsky AS, Zamel N. The effects of air pollution on allergic bronchial responsiveness. Clin Exp Allergy 22:667–672 (1992).
48. Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents [See Comments]. Am J Respir Crit Care Med 158:352–357 (1998).
49. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life [See Comments]. Br Med J 309:90–93 (1994).
50. Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. J Epidemiol Community Health 40:121–129 (1986).
51. Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. Eur Respir J 8:349–356 (1995).
52. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates [See Comments]. N Engl J Med 332:133–138 (1995).
53. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. Am J Epidemiol 139:1139–1152 (1994).
54. Cunningham J, Dockery DW, Speizer FE. Race, asthma, and persistent wheeze in Philadelphia schoolchildren. Am J Public Health 86:1406–1409 (1996).
55. Peat JK, Tovey CM, Mellis CM, Leeder SR, Woolcock AJ. Importance of house dust mite and Alternaria allergens in childhood asthma: an epidemiological study in two climatic regions of Australia. Clin Exp Allergy 23:812–820 (1993).
56. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, Woolcock AJ. House dust mite allergens. A major risk factor for childhood asthma in Australia. Am J Respir Crit Care Med 153:141–146 (1996).
57. Pollart SM, Chapman MD, Fiocco GP, Rose G, Platts-Mills TA. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. J Allergy Clin Immunol 83:875–882 (1989).
58. Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TA. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude. Tickling the dragon's breath [See Comments]. Am J Respir Crit Care Med 151:1388–1392 (1995).
59. Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. Alternaria as a major allergen for asthma in children raised in a desert environment. Am J Respir Crit Care Med 155:1356–1361 (1997).
60. Burge HA, Rogers CA. Outdoor allergens. Environ Health Perspect 108(suppl 4):653–659 (2000).
61. Maelzer DA. Water, temperature and house-dust mites. In: Mites, Asthma and Domestic Design: Proceedings of a Conference, 15 March 1993, Sydney, Australia, 1993;9–18.
62. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma [See Comments]. N Engl J Med 336:1356–1363 (1997).
63. Gelber LE, Seltzer LH, Bouzoukis JK, Pollart SM, Chapman MD, Platts-Mills TA. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. Am Rev Respir Dis 147:573–578 (1993).
64. Call RS, Smith TF, Morris E, Chapman MD, Platts-Mills TA. Risk factors for asthma in inner city children [See Comments]. J Pediatr 121:862–866 (1992).
65. Chew GL, Burge HA, Dockery DW, Muilenberg ML, Weiss ST, Gold DR. Limitations of a home characteristics questionnaire as a predictor of indoor allergen levels. Am J Respir Crit Care Med 157:1536–1541 (1998).
66. Simon HU, Grotzer M, Nikolaizik WH, Blaser K, Schoni MH. High altitude climate therapy reduces peripheral blood T lymphocyte activation, eosinophilia, and bronchial obstruction in children with house-dust mite allergic asthma. Pediatr Pulmonology 17:304–311 (1994).
67. Piacentini GL, Martinati L, Fornari A, Comis A, Carcereri L, Boccagni P, Boner AL. Antigen avoidance in a mountain environment: influence on basophil releasability in children with allergic asthma. J Allergy Clin Immunol 92:644–650 (1993).
68. Ehnert B, Lau-Schadendorf S, Weber A, Buettner P, Schou C, Wahn U. Reducing domestic exposure to dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. J Allergy Clin Immunol 90:135–138 (1992).
69. Carswell F, Birmingham K, Oliver J, Crewes A, Weeks J. The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children—a double-blind controlled trial. Clin Exp Allergy 26:386–396 (1996).
70. Kuehr J, Frischer T, Meinert R, Barth R, Forster J, Schraub S, Urbanek R, Karmaus W. Mite allergen exposure is a risk for the incidence of specific sensitization. J Allergy Clin Immunol 94:44–52 (1994).
71. Wickman M, Korsgaard J. Transient sensitization to house-dust mites: a study on the influence of mite exposure and sex. Allergy 51:511–513 (1996).
72. Rowntree S, Cogswell JJ, Platts-Mills TA, Mitchell EB. Development of IgE and IgG antibodies to food and inhalant allergens in children at risk of allergic disease. Arch Dis Child 60:727–735 (1985).
73. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study [See Comments]. N Engl J Med 323:502–507 (1990).
74. Brenner RJ. Preparing for the 21st century: research methods in developing management strategies for arthropods and allergens in the structural environment. In: Proceeding of the 1st International Conference on Insects Pests in the Urban Environment (Wildey KB, Robinson WH, eds). Exeter, UK:BPCC, Weatons Ltd, 1993;57–69.
75. Gordon DG. The Complete Cockroach. Berkeley, CA:Ten Speed Press, 1996.
76. O'Connor GO, Gold DR. Cockroach allergy and asthma in a 30-year old man. Environ Health Perspect 107:243–247 (1999).
77. Cochran DG. Relevance of resistance ratios to operational control in the German cockroach (*Dictyoptera, Blatelidae*). J Econ Ent 89:318–321 (1996).
78. Hemingway J, Small GJ. Resistance mechanisms in cockroaches - the key to control strategies. In: Proceedings of the 1st International Conference on Insect Pests in the Urban Environment (Wildey KB, Robinson WH, eds). Exeter, UK:BPCC, Weatons Ltd, 1993;141–152.
79. Schou C. Defining allergens of mammalian origin. Clin Exp Allergy 23:7–14 (1993).
80. Pollart SM, Smith TF, Morris EC, Gelber LE, Platts-Mills TA, Chapman MD. Environmental exposure to cockroach allergens: analysis with monoclonal antibody-based enzyme immunoassays. J Allergy Clin Immunol 87:505–510 (1991).
81. de Blay F, Sanchez J, Hedelin G, Perez-Infante A, Verot A, Chapman M, Pauli G. Dust and airborne exposure to allergens derived from cockroach (Blattella germanica) in low-cost public housing in Strasbourg (France). J Allergy Clin Immunol 99:107–112 (1997).
82. Bernton HS, Brown H. Preliminary studies of the cockroach. Allergy 35:506–513 (1964).
83. Kang B. Study on cockroach antigen as a probable causative agent in bronchial asthma. J Allergy Clin Immunol 58:357–365 (1976).
84. Sarpong SB, Hamilton RG, Eggleston PA, Adkinson NF Jr. Socioeconomic status and race as risk factors for cockroach allergen exposure and sensitization in children with asthma. J Allergy Clin Immunol 97:1393–1401 (1996).
85. Gold DR, Burge HA, Carey V, Milton DK, Platts MT, Weiss ST. Predictors of repeated wheeze in the first year of life. The relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. Am J Respir Crit Care Med 160:227–236 (1999).
86. Williams L, Reinfreid P. Eradication of cockroaches does not rapidly reduce cockroach (CR) allergen in vacuumed dust [Abstract]. J Allergy Clin Immunol 101:s157 (1998).
87. De Andrade AD, Birnbaum J, Magalon C, Magnol JP, Lanteaume A, Charpin D, Vervloet D. Fel d I levels in cat anal glands. Clin Exp Allergy 26:178–180 (1996).
88. Warner JA. Environmental allergen exposure in homes and schools [Editorial]. Clin Exp Allergy 22:1044–1045 (1992).
89. Custovic A, Simpson A, Pahdi H, Green RM, Chapman MD, Woodcock A. Distribution, aerodynamic characteristics, and removal of the major cat allergen Fel d 1 in British homes. Thorax 53:33–38 (1998).
90. Dybendal T, Elsayed S. Dust from carpeted and smooth floors. VI: Allergens in homes compared with those in schools in Norway. Allergy 49:210–216 (1994).
91. Bollinger ME, Eggleston PA, Flanagan E, Wood RA. Cat antigen in homes with and without cats may induce allergic symptoms. J Allergy Clin Immunol 97:907–914 (1996).
92. Sicherer SH, Wood RA, Eggleston PA. Determinants of airway responses to cat allergen: comparison of environmental challenge to quantitative nasal and bronchial allergen challenge. J Allergy Clin Immunol 99:798–805 (1997).
93. Norman PS, Ohman JL Jr, Long AA, Creticos PS, Gefter MA, Shaked Z, Wood RA, Eggleston PA, Hafner KB, Rao P, et al. Treatment of cat allergy with T-cell reactive peptides. Am J Respir Crit Care Med 154:1623–1628 (1996).
94. Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TA. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. J Allergy Clin Immunol 96:449–456 (1995).
95. Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. Clin Exp Allergy 19:419–424 (1989).
96. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy 29:611–617 (1999).
97. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 158:115–120 (1998).
98. Avner DB, Perzanowski MS, Platts-Mills TA, Woodfolk JA. Evaluation of different techniques for washing cats: quantitation of allergen removed from the cat and the effect on airborne Fel d 1 [See Comments]. J Allergy Clin Immunol 100:307–312 (1997).
99. van der Heide S, van Aalderen WM, Kauffman HF, Dubois AE, de Monchy JG. Clinical effects of air cleaners in homes of asthmatic children sensitized to pet allergens. J Allergy Clin Immunol 104:447–451 (1999).
100. Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The

effect of cat removal on allergen content in household-dust samples. J Allergy Clin Immunol 83:730–734 (1989).
101. Vanto T, Koivikko A. Dog hypersensitivity in asthmatic children. A clinical study with special reference to the relationship between the exposure to dogs and the occurrence of hypersensitivity symptoms. Acta Paediatr Scand 72:571–575 (1983).
102. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol 103:415–420 (1999).
103. Michel O, Kips J, Duchateau J, Vertongen F, Robert L, Collet H, Pauwels R, Sergysels R. Severity of asthma is related to endotoxin in house dust. Am J Respir Crit Care Med 154:1641–1646 (1996).
104. Michel O, Ginanni R, Duchateau J, Vertongen F, Le Bon B, Sergysels R. Domestic endotoxin exposure and clinical severity of asthma. Clin Exp Allergy 21:441–448 (1991).
105. Braun-Fahrlander C, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS, Vuille JC, Wuthrich B. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. Clin Exp Allergy 29:28–34 (1999).
106. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 149:358–364 (1994).
107. Chew GL, Higgins KM, Milton DK, Burge HA. The effects of carpet fresheners and other additives on the behaviour of indoor allergen assays. Clin Exp Allergy 29:470–477 (1999).
108. Platts-Mills TA, Woodfolk JA, Chapman MD, Heymann PW. Changing concepts of allergic disease: the attempt to keep up with real changes in lifestyles. J Allergy Clin Immunol 98:S297–S306 (1996).